REMARKS

The present invention relates in part to methods for diagnosing stroke or cerebral injury in subjects. These methods comprise measuring at least the 108 amino acid BNP precursor or one or more of its related markers, and determining whether the marker(s) measured correlate to the occurrence or nonoccurrence of a stroke or cerebral injury.

The specification has been amended to comply with the usage of trademarks requested by the Examiner. Accordingly, the amendments raise no issue of new matter.

Claims 32-38 are pending herein, and by the present amendments new claims 39-41 are added. These new claims are included within the scope of claim 38, and raise no issue of new matter.

Claims 32, 35, 36, and 38 are amended herein in an effort to clarify the subject matter of the claims for the benefit of the Examiner. In claims 32, 35, and 36, Applicants have attempted to comply with the Examiner's request that the names used for certain markers be further elaborated upon using art-recognized alternate names. These amendments raise no issue of new matter.

In claims 32 and 38, Applicants have replaced the phrase "immunologically detectable fragment thereof" with the phrase "markers related thereto." These amendments are fully supported by the specification as filed and raise no issue of new matter. For example, paragraph [0018] defines the term "related marker."

Applicants have made this amendment solely to advance prosecution of the present claims. As discussed hereinafter, a parent to the present application was recently the subject of a Decision on Appeal with respect to the use of the phrase "markers related thereto" in precisely the same manner as it is being used in the present claims. In that Decision on Appeal, a rejection under the Written Description requirement directed to this phrase was reversed. A copy of this Decision on Appeal accompanies this response.

Applicants request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

1. Specification

Applicants have amended the specification to comply with the usage of trademarks requested by the Examiner. Accordingly, withdrawal of this objection is respectfully requested.

2. Claim Objection

Applicants respectfully submit that the Examiner is incorrect that claims 33-38 are in improper form in reciting "A method according to claim 'x.'" The language to which the Examiner objects indicates that the claim refers back to, and further limits, claim x, in accordance with 37 C.F.R. § 1.75. Applicants note that MPEP 608.01(n) specifically describes the use of the indefinite article in the context of multiple dependent claims. There is nothing of record to indicate that the skilled artisan would understand such language in the context of multiple dependent claims, but somehow would not reasonably understand the very same language in a singular dependent claim. A search of the USPTO issued patent database using the Delphion as a search system identified 113,873 patents with claims that recite "A method according to claim." The language requested by the Examiner was found in 139,153 patents. These accuracy of these numbers is shown by a combination search ("method according to claim") which identified 242,930 patents. This evidence shows that Applicant's use of the definite article in the manner at issue is commonly accepted by the USPTO.

In view of the foregoing, Applicants respectfully traverse this objection and request that it be withdrawn.

3. Claim Objection

Applicants respectfully submit that the Examiner is incorrect that the terms "TRAIL," "TWEAK," and "BNP" are acronyms. These are, instead, *names* for proteins that are well known in the art. As evidence of this fact, Applicants have submitted herewith a printout from the Human Protein Reference Database in which each of these names appear, not as acronyms, but under the heading of "alternate names" (BNP and TWEAK) or as the main accepted name (TRAIL). Applicants do not disagree that the term "CT" may be considered an abbreviation for computed tomography, as noted in the specification at paragraph [0010].

In order to advance prosecution and to clarify the claimed subject matter for the benefit of the Examiner, Applicants have amended the claims in accordance with the Examiner's suggestions. In view of the foregoing, Applicants respectfully request that the objection be withdrawn.

4. 35 U.S.C. §112, Second Paragraph (definiteness)

Applicants respectfully traverse the rejection of claims 32-38 as allegedly failing to satisfy the definiteness standard of 35 U.S.C. §112, second paragraph.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more").

Moreover, as the Board of Patent Appeals and Interferences recently pointed out, even a "lack of clarity" is insufficient to establish indefiniteness. Rather, the claim must rise to the level of being insolubly ambiguous:

> The threshold for indefiniteness is very high: the claim must be "insolubly ambiguous". . . . If one of skill in the art would understand the scope of the claim when read in light of the specification, then the claim complies with § 112(2). Claims need not be models of clarity. As long as the meaning is discernible, then even if construction is difficult and the result equivocal, the claim is nevertheless definite. Exxon Research & Eng'g Co., 265 F.3d at 1375, 60 USPQ2d at 1276; All Dental Prodx LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 779-80, 64 USPQ2d 1945, 1949 (Fed. Cir. 2002) (no indefiniteness despite the lack of clarity).

Ex Parte Hicks, 2000 WL 33673734, *4 (Bd. Pat. App & Interf.).

Before amendment, claim 32 referred to the 108 amino acid BNP precursor or an immunologically detectable fragment thereof. The Examiner asserts that this renders the claim indefinite because "[t]he specification does not teach examples of 'fragments thereof'" and because such immunologically detectable fragments allegedly "reads on any single amino acid." Office Action, page 5. No support for this personal opinion of the Examiner is offered, nor is it

explained why the skilled artisan would not understand the scope of the claims. Indeed, the skilled artisan understands that a detectable epitope on a target protein is on the order of 8 amino acids, and would not consider detecting a single amino acid to be within the scope of the phrase "immunologically detectable fragments" of a target protein.

Moreover, the Examiner's personal opinion appears to be directed to the question of operability of the claims. Applicants note that immunoassay methods are generally unlikely to work at 100°C, when frozen in liquid nitrogen, at pH 1, or in the presence of 8M urea, as such conditions are not particularly hospitable to immunoassays. The question of definiteness is not measured by whether or not certain far fetched scenarios may be constructed in which the invention will not work. Rather, the question of definiteness is measured by whether the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention.

Applicants submit that the Examiner's rejection is based on an unsupported personal opinion and does not comport with the reasonableness standard inherent in any definiteness analysis, and that the claims as originally written meet the definiteness standard of 35 U.S.C. §112, second paragraph.

Nevertheless, the present claims have been amended to refer to performing an assay by contacting a subject's test sample with an antibody that binds the 108 amino acid BNP precursor or markers "related" thereto. As defined in the specification, the term "related marker" refers to one or more fragments of a particular marker that may be detected as a surrogate for the marker itself. Specification, paragraph [0018].

As noted above, a parent to the present application was recently the subject of a Decision on Appeal. The claims of the parent application were directed to a method of determining the diagnosis of a stroke, as are the present claims. Decision on Appeal 2007-0628, page 3 (copy attached herewith). Moreover, the claims of the parent application used the phrase "markers related thereto" in precisely the same manner as it is being used in the present claims. *Id.* On page 5 of the Decision on Appeal, the Board of Patent Appeals and Interferences agreed with the present Applicants that there is no *per se* requirement that fragments of a known protein must be

disclosed in the specification.

Applicants respectfully submit that the present claims, when read in the light of the specification, reasonably apprise those skilled in the art of the scope of the invention. Because the definiteness standard of 35 U.S.C. §112, second paragraph, demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

5. 35 U.S.C. §112, First Paragraph (written description)

Applicants respectfully traverse the rejection of claims 32-38 as allegedly failing to satisfy the written description standard of 35 U.S.C. §112, first paragraph.

Before the amendments presented herein, the claims referred to a method of determining the occurrence or nonoccurrence of a stroke in a subject by: performing an assay by contacting a test sample from the subject with an antibody that binds to the 108 amino acid BNP precursor or an immunologically detectable fragment thereof. The Examiner asserts that the specification fails to meet the written description standard because "[n]either the specification nor the claims teach how to define or obtain "immunologically detectable fragment thereof." Applicants note that the present submission amends the claims to replace the phrase "immunologically detectable fragment thereof" with the phrase "markers related thereto."

For the reasons discussed below, Applicants respectfully submit that the Examiner's comments do not establish that the claims do not meet the written description standard of 35 U.S.C. §112, first paragraph, either for the claims as originally presented, or for the claims as amended herein.

As previously noted, a parent to the present application was recently the subject of a Decision on Appeal with respect to the use of the phrase "markers related thereto" in precisely the same manner as it is being used in the present claims. As Applicants have also noted, the Board of Patent Appeals and Interferences reversed the rejection under the Written Description requirement directed to this phrase. In the appeal of the parent case, the present Applicants argued as follows. These arguments are equally applicable to the present claims.

The present specification provides a clear and unequivocal definition for the term "related marker." Unambiguously, the specification states in paragraph [0018] that "the term 'related

marker' as used herein refers to one or more fragments of a particular marker that may be detected as a surrogate for the marker itself" (emphasis added). In the present case, the "related markers" recited in the claims are all characterized by their structural relationship to the claimed parent marker, the structure of which is well known in the art. In the case of the BNP precursor that is the species at issue in the rejection, the structure has long been available to the public (since 1989). The artisan understands that, because a detectable epitope on a target protein is on the order of 8 amino acids, and that protein assays such as immunoassays can detect both an intended target polypeptide, and "related markers" containing the epitope(s) necessary to bind to the antibody or antibodies used in the assay.

Imposing a *per se* requirement that such fragments must be disclosed in the specification is contrary to the established law. Indeed, the Federal Circuit has emphasized again "that there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure":

> [I]t is the binding precedent of this court that Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. Thus, '[w]hen the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh.' Rather, we explained that: 'The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.'

Falkner v. Inglis, 448 F.3d 1357, 1367-68 (Fed. Cir. 2006) (emphasis in original).

During prosecution of the parent application, Appellants submitted a declaration by Dr. Kenneth Buechler explaining why measurement of polypeptides that are "related" to a particular marker of interest is well understood by those of skill in the art, and why the language of the claims does nothing more than reflect the realities concerning protein assays. The Buechler declaration is submitted with this response so that it may be of record in the present application

as well. Applicants respectfully submit that an adequate written description may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. Moreover, the term "related markers" is clearly defined in the specification in a manner that comports with the well understood realities in the art of protein assays. Given the nature and scope of the invention at issue, and the scientific and technologic knowledge already in existence, the present specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. The written description requirement demands no more.

After considering these arguments in the parent case, the Board of Patent Appeals and Interferences stated the following (emphasis added):

> The Examiner focuses on the recitation in the claims, in addition to the specified protein markers, of "marker(s) related thereto." The Examiner notes that the Specification defines "related marker" to mean "fragments of a particular marker that may be detected as a surrogate for the marker itself" (Answer 5) but argues that that definition is an inadequate description because the specification does not define "what the fragments of S100β and caspase-3 are" (id.).
>
> Appellants argue that "the 'related markers' [are] all characterized by their structural relationship to a parent marker, the structure of which is well known" (Br. 12) and that "[a]s the proteins recited in the claims are all known proteins having known sequences, the identity of various 'related' polypeptides (e.g., the corresponding 'precursor' and 'NT-pro' forms) may be easily ascertained from ... a standard database" (id. at 13-14).
>
> We agree with Appellants that the Examiner has not shown that the "related markers" recited in the claims are not adequately described. The Examiner argues that the Specification's definition of related markers is "inclusive and nonlimiting and thus is not limited to fragments" (Answer 9). We disagree. "Related marker" is expressly defined to mean "fragments of a particular marker that may be detected as a surrogate for the marker itself" (Specification 5).
>
> Appellants have asserted that all the proteins recited in the claims are known in the art, and the Examiner has not disputed that assertion. **Thus, the "related markers" recited in the claims are merely fragments of known proteins. We agree with Appellants that the sequences of known proteins, and fragments of them, are readily available to those skilled in the art. "[T]here is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure."** Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). "Indeed, [such a requirement], if one existed, would serve no goal of the written

description requirement." Id. at 1368, 79 USPQ2d at 1008.

> The Examiner has not established that the claims are unpatentable under 35 U.S.C. § 112, first paragraph. The rejection of claims 45, 47, 50, 53-69, and 73 for lack of adequate written description is reversed.

Applicants respectfully submit that, as in the parent case, the specification reasonably conveys to the skilled artisan that Applicants were in possession of the claimed invention at the time the present application was filed. Because the written description requirement demands no more, Applicants request that the rejections be reconsidered and withdrawn.

6. 35 U.S.C. §112, First Paragraph (written description)

Applicants respectfully traverse the rejection of claims 32-38 as allegedly failing to satisfy the written description standard of 35 U.S.C. §112, first paragraph.

The claims as amended herein refer to a method of determining the occurrence or nonoccurrence of a stroke in a subject by: performing an assay by contacting a test sample from the subject with an antibody that binds to the 108 amino acid BNP precursor or one or more markers related thereto.

The Examiner asserts that the specification "does not provide a method wherein the single 108-residue BNP precursor or an immunologically detectable fragment thereof is employed to detect stroke (occurrence or nonoccurrence)." Office Action, page 8. Applicants respectfully submit that this is incorrect.

In paragraph [0015], the specification states the following:

> In a first aspect, the invention discloses methods for determining a diagnosis or prognosis related to stroke, or for differentiating between types of strokes and/or TIA. These methods comprise analyzing a test sample obtained from a subject for the presence or amount of one or more markers for neural tissue injury. These methods can comprise identifying one or more markers, the presence or amount of which is associated with the diagnosis, prognosis, or differentiation of stroke and/or TIA. Once such marker(s) are identified, the level of such marker(s) in a sample obtained from a subject of interest can be measured. In certain embodiments, these markers can be compared to a level that is associated with the diagnosis, prognosis, or differentiation of stroke and/or TIA. By correlating the subject's marker level(s) to the diagnostic marker level(s), the presence or absence

> of stroke, the probability of future adverse outcomes, *etc.*, in a patient may be rapidly and accurately determined.

In paragraph [0019], the specification states the following (emphasis added):

> Preferred markers for the diagnosis and/or prognosis of stroke include caspase-3, cathepsin D, α-spectrin, D-dimer, IL-1ra, NCAM, c-tau, neuropeptide Y, Tweak, c-Tau, IL-1ra, MCP-1, S100β, MMP-9, vWF, **BNP**, CRP, NT-3, VEGF, CKBB, MCP-1 Calbindin, thrombin-antithrombin III complex, IL-6, IL-8, myelin basic protein, tissue factor, GFAP, and CNP, **or markers related thereto**. Each of these terms is defined hereinafter.

In paragraph, [0096], the specification describes the known relationship of various fragments of the BNP precursors, noting for example that mature BNP (the fragment containing residues 77-108) and NT-proBNP (the fragment containing residues 1-76) are created from pro-BNP by the same cleavage event:

> For example, human BNP is derived by proteolysis of a 108 amino acid precursor molecule, referred to hereinafter as BNP_{1-108}. Mature BNP, or "the BNP natriuretic peptide," or "BNP-32" is a 32 amino acid molecule representing amino acids 77-108 of this precursor, which may be referred to as BNP_{77-108}. The remaining residues 1-76 are referred to hereinafter as BNP_{1-76}.

In paragraph [0099], the specification states the following:

> While mature BNP itself may be used as a marker in the present invention, the prepro-BNP, BNP_{1-108} and BNP_{1-76} molecules represent BNP-related markers that may be measured either as surrogates for mature BNP or as markers in and of themselves. In addition, one or more fragments of these molecules, including BNP-related polypeptides selected from the group consisting of BNP_{77-106}, BNP_{79-106}, BNP_{76-107}, BNP_{69-108}, BNP_{79-108}, BNP_{80-108}, BNP_{81-108}, BNP_{83-108}, BNP_{39-86}, BNP_{53-85}, BNP_{66-98}, BNP_{30-103}, BNP_{11-107}, BNP_{9-106}, and BNP_{3-108} may also be present in circulation.

And, in Table 20 on page 114, the specification provides experimental evidence that BNP is significantly increased in subjects in both the 0-6 hour and 6-24 hour time frames following acute presentation with stroke.

Applicants respectfully submit that, contrary to the Examiner's assertion, the specification not only provides "a method wherein the single 108-residue BNP precursor or an

immunologically detectable fragment thereof is employed to detect stroke," the specification provides and extensive description of each step in such a method.

The Examiner refers to a discussion from Applicants' specification stating the fact that BNP is nonspecific, in that it is also elevated in other conditions, and that "a single marker may have limited use and further teaches that the data relating to levels of various multiple markers for diseased and non-diseased patients may be used to develop a panel of marker[s]." Office Action, page 8. This appears to indicate the Examiner's belief that only "specific markers" (that is, markers that are only affected by a specific disease state) can be used in diagnostic methods. Such a belief is not consistent with the use of biomarkers generally in the art.

While one might desire to have available such "specific markers" for a particular disease or condition, that is often not possible. Fortunately, even nonspecific markers can be useful clinically when in the hands of the skilled artisan, as the skilled artisan does not use diagnostic tests in an informational vacuum. Rather, diagnostic tests are used by skilled medical personnel in concert with other available medical indicia related to a subject.

For example, assays that detect BNP and NT-proBNP, and proBNP assays are FDA-approved for use in the diagnosis of heart failure. But, as the Examiner correctly notes, BNP is also a marker in acute coronary syndromes. Moreover, as taught in the present application, BNP is also a marker in stroke. Despite the fact that BNP and its related markers may be elevated in multiple diseases, it is still used in evaluating patients by those of skill in the art on a daily basis. Similarly, D-dimer is not a specific marker of pulmonary embolism. *See, e.g.*, Indik and Alpert, *Prog. Cardiovasc. Dis.* 42: 261-272, 2000, page 262 ("Since D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis in the body, the specificity of all DD assays is expected to be low") (copy attached as part of an IDS). Nevertheless, it is an FDA-approved test used routinely by artisans in the evaluation of pulmonary embolism.

This is not meant to be an exhaustive list, but rather is intended to point out that the state of the prior art plainly indicates that markers need not be elevated in a single specific condition for such markers to be useful to the artisan in clinical diagnosis. Few, if any, such definitive tests exist. The term "diagnosis" refers to a relative probability that a certain disease is present in the subject, and not the ability of a "specific marker" to give a definitive yes/no answer to the

existence of a disease. Tests are routinely used to "rule in" a diagnosis, or to "rule out" a diagnosis by signaling an increased or decrease probability of a particular diagnosis, particularly when used in concert with other available medical indicia. This is true whether or not there are other conditions in which the markers are also elevated.

Applicants respectfully submit that, as in the parent case, the specification reasonably conveys to the skilled artisan that Applicants were in possession of the claimed invention at the time the present application was filed. Because the written description requirement demands no more, Applicants request that the rejections be reconsidered and withdrawn.

7. 35 U.S.C. § 112, first paragraph (enablement)

Applicant respectfully traverses the rejection of claims 32-38 as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

Initially, Applicants note that the rejection has been applied to methods that use a BNP assay alone for determining the occurrence or nonoccurrence of a stroke. The Examiner acknowledges that the specification enables a method in which a BNP assay is used in concert with other assays in a "panel" approach. Office Action, page 9. Applicants again note that in Table 20 on page 114, the specification provides experimental evidence that BNP is significantly increased in subjects in both the 0-6 hour and 6-24 hour time frames following acute presentation with stroke. So, to the extent that the rejection rests on an incorrect belief that the specification does not provide exemplary data for determining the occurrence or nonoccurrence of stroke in a subject by performing a single assay for the 108-residue BNP precursor or an immunologically detectable fragment thereof is employed to detect stroke, the rejection is improperly founded.

Moreover, the Examiner's comments in this regard appear to conflate what is exemplified in the specification with what is enabled by the specification. The presence or absence of working examples is but one factor in a proper enablement analysis.

Furthermore, the Examiner's reliance on Diamond *et al.*, US 2005/0181386, for the proposition that the cited publication "teach[es] that no single marker exists for the detection of stroke" (Office Action, page 12) is misplaced. First of all, the Examiner is incorrect in asserting that Diamond *et al.* is "prior art." It is not. Second, statements made by third party which have

no knowledge of actual experimental results contained in the specification should have no bearing on an enablement analysis. Diamond *et al.* plainly falls into this category.

Furthermore, it is plain that following Applicants' filing date, the art has confirmed the teachings of the claimed invention. For example, *Nakagawa et al., Cerebrovasc. Dis.* 19:157-164 (2005) and Yip *et al., Circ. J.* 70: 447-52, 2006, confirm that BNP and NT-proBNP are each elevated in acute ischemic stroke (copy of each attached as part of an IDS).

In addition to the foregoing comments, Applicants will attempt to address the Examiner's remarks in the context of the various *Wands* factors below.

A. The nature of the invention

The present invention is related to the use of biomarker measurements to determine the occurrence or nonoccurrence of a stroke.

B. The state of the prior art

The state of the prior art is one of common usage of biomarkers generally for medical diagnosis, with the caveat that measurement of BNP and its related markers in a body fluid sample have not been described for use in determining the occurrence or nonoccurrence of stroke.

As noted above, the Examiner refers to a discussion of stroke diagnostic methods from Diamond *et al.*, US 2005/0181386. However, this publication is not prior art to the present application, and the statements to which the Examiner refers were made without any knowledge of the teachings and data provided in the present application. As such, Applicants respectfully submit it is not relevant to an understanding of the prior art.

The Examiner also refers to the fact that BNP and its related markers are also elevated in other conditions. Office Action, page 10. This appears to indicate the Examiner's belief that only "specific markers" (that is, markers that are only affected by a specific disease state) can be used in diagnostic methods. For example, the Examiner states that "it is not clear how the detection of only BNP in any subject would necessarily be indicative of stroke and not some other condition or disorder." Office Action, page 12. Such a belief is not consistent with the use of biomarkers generally in the art.

While one might desire to have available "specific markers" for a particular disease or condition, that is typically not the reality. Fortunately, even nonspecific markers can be useful clinically when in the hands of the skilled artisan, as the skilled artisan does not use diagnostic tests in an informational vacuum. Rather, diagnostic tests are used by skilled medical personnel in concert with other available medical indicia related to a subject.

As discussed above in the portion of this submission dealing with written description, the state of the prior art plainly indicates that markers need not be elevated in a single specific condition for such markers to be useful to the artisan in clinical diagnosis. Few, if any, such definitive tests exist. Even for CT scan, which is often the best test available for stroke diagnosis at a particular hospital, a number of "false positive" and "false negative" results occur and must be tolerated. *See, e.g.*, Mullins *et al., Radiology* 224: 353-60, 2002, table 5 (copy attached as part of an IDS). Clearly, this does not mean that CT is not a useful diagnostic test for stroke, despite the fact that the Examiner also seeks to denigrate the use of CT scan in stroke. *See, e.g.*, Office Action, page 13 ("The use of CT to distinguish the cause of brain damage has not been taught... [and] CT cannot definitively identify stroke".

The Examiner appears to appreciate that term "diagnosis" refers to assigning a relative probability that a certain disease is present in the subject, and not the ability of a "specific marker" to give a definitive yes/no answer to the existence of a disease. Tests are routinely used to "rule in" a diagnosis, or to "rule out" a diagnosis by signaling an increased or decrease probability of a particular diagnosis, particularly when used in concert with other available medical indicia, and any test (or even combination of tests) will have a level of sensitivity and specificity that typically does not meet the ideal of 100% each. If diagnostic tests needed to meet the standard that the Examiner applies – to be able to <u>definitively</u> identify the presence or absence of disease – both patients and physicians would be in dire straits indeed.

The Examiner also refers to a general text concerning "characteristics [that] need to be considered in the development of any suitable diagnostic assay," such as sensitivity, true-positive rate, false-negative rate, specificity, true-negative rate, false-positive rate, *etc.* Office Action, page 13. Applicants submit that this general text is emblematic of the fact that diagnostic tests are commonly developed and used in the art, and that the artisan understands well the various

characteristics that should be considered when determining how such tests should be used in patient care. At most, such a discussion amounts at most to a list of various difficulties which might be encountered in practice of the invention, which is not a sufficient evidentiary basis for questioning the enablement of a presumptively enabling disclosure. *Ex parte Hicks*, 2000 WL 33673734 (Bd. Pat. App. & Interf., 2000); *Ex parte Miyada*, http://www.uspto.gov/web/offices/dcom/bpai/decisions/fd973535.pdf, page 5 (Bd. Pat. App. Int. 1997). The Examiner's comments also do not negate the extensive teachings in the specification and the experimental evidence provided that BNP is significantly increased in subjects in both the 0-6 hour and 6-24 hour time frames following acute presentation with stroke.

In addition, Applicants also note that such "characteristics" presumably would need to be considered by an artisan practicing the claimed invention, whether the artisan performs only a BNP, or uses BNP in a panel approach. Why the Examiner considers such "characteristics" to present more of a problem when only one assay is performed (which the Examiner argues is not enabled) as opposed to when several assays are performed (which the Examiner states is enabled) is unclear and unexplained.

C. The relative level of skill in the art

The skill in the art is extremely high. The skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis and prognosis of patients, and also has extensive experience in the generation and characterization of antibodies for use in such tests. As noted above with regard to the state of the art, the skilled artisan is well aware of the various difficulties that might be encountered in practice. The artisan also is well prepared to address any of such difficulties as part of practicing the claimed methods, and understands that the required methods are routine in the art.

D. The quantity of experimentation necessary

The Examiner acknowledges that the specification is enabling for a method in which both a BNP assay is used in concert with other assays in a "panel" approach. Office Action, page 11. Applicants respectfully submit that the quantity of experimentation required to practice the invention in which only a BNP assay is performed for determining the occurrence or nonoccurrence of a stroke is not greater than that required to practice the identical method in

which a BNP assay is used in a panel approach, as all of the methods necessary would be essentially identical.

E. The predictability of the art

In the present case, the methods to be followed are all routine and predictable; the only factor required to practice the claimed invention is the understanding of which markers should be pursued, an issue that is solved by reference to the present specification and claims.

F. The amount of direction or guidance

The specification provides the artisan with suitable methods for each and every step in the process of practicing the claimed methods, from generating antibodies, to preparing assays, and to selection of subjects and data analysis.

G. The presence or absence of working examples

As discussed above, the rejection has failed to consider that the specification does contain working examples and data demonstrating that BNP is individually significantly increased in subjects in both the 0-6 hour and 6-24 hour time frames following acute presentation with stroke.

H. The breadth of the claims

The claims are circumscribed in their breadth, in that they refer to methods for distinguishing the occurrence or nonoccurrence of stroke that comprise performing assays for the specified biomarker(s).

The Examiner's comments concerning breadth indicate that the claims "do not limit the population to be tested," and that the methods "include determining the mere presence of the markers." Office Action, page 6. Applicants note that such comments presumably apply to the claimed invention, whether the artisan performs only a BNP assay, or a BNP assay is used in concert with other assays in a "panel" approach. Why the Examiner considers such "breadth" to present more of a problem when only one assay is performed (which the Examiner argues is not enabled) as opposed to when both assays are performed (which the Examiner states is enabled) is unclear and unexplained.

As far as "determining the mere presence of the markers," the artisan is well aware that assays may be configured to provide a positive result only when a particular threshold is reached. Even lay individuals have experience with such assays, typically in the form of over-the-counter pregnancy tests that deliver a positive result only when hCG exceeds some predetermined limit. *See, e.g.*, U.S. Patent No. 5,028,535. Such assays can provide only a qualitative "present/absent" type of result, and do not provide any information concerning the "amount" of the analyte of interest. Indeed, the same result is obtained whether the analyte is present at a level required to generate a positive result, at 10 times that level, at 100 times that level, or at even larger multiples of that level. Despite not providing results in the form of an "amount" of analyte, such tests can provide the artisan with the information necessary to practice the present claims.

I. Conclusion

In the present case, the skilled artisan can, by simply following the extensive detailed guidance in the specification, perform the claimed methods using nothing more that routine experimentation. In contrast, the rejection fails to consider the knowledge available in the art, being based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that *might* be encountered in practice. As such, the rejection does not present a sufficient basis for rejecting a claim under the enablement requirement.

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

7. Obviousness-type double patenting

With regard to the Examiner's provisional rejection for Obviousness-type double patenting, Applicants note that no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. See MPEP 804 (I)(B) (The "provisional" double patenting rejection

should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.") In the event that other rejections of the present claims are successfully overcome by the current communication, withdrawal of the instant provisional rejection would be appropriate. Applicants authorize the examiner to follow MPEP 804 (I)(B) and allow the case without issuing a further Office Action should the provisional obviousness type-double patenting rejection be the sole remaining issue in the case.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date 06/18/2007

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